Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/031,008	LIBUTTI ET AL.	
	Examiner	Art Unit	
	MICHAEL BURKHART	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 February 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Michael Burkhart/
Primary Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because: Claims 2, 4, 16, 18, 22 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (U.S. patent 6,638,502, of record) in view of Restifo et al (U.S. patent 5,733,548, of record). This rejection is maintained for reasons made of record in the Office Actions dated 2/22/2006, 11/9/2006, 6/13/2007, 2/8/2008, 11/13/2008, and for reasons set forth below.

Response to Arguments

Applicant's arguments filed 2/17/2009 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the results of the instant invention are surprising in light of the teachings of Gabathuler et al regarding the E3/19K protein; 2) Restifo et al involve targeting a peptide to the ER in order to associate it with MHC molecules, producing a complex that is displayed on the cell surface and thus not secreted; 3) the art does not hint that proteins attached to an E19 signal sequence would be secreted; 4) Li et al teach that the signal sequence is not the E19 signal sequence; 5) the present rejection is based upon the assumption that all signal sequences are the same, which is contradicted by the prior art; 6) Neither Restifo nor Li et al teach that the E19 signal sequence will predictably express a secreted form of an antiangiogenic protein commensurate in scope with the claims; 7) nothing in the prior art suggest arriving at a composition that reduces tumor growth when administered systemically; 8) Griscelli et al does make up for the deficiencies of Restifo and Li et al.

Regarding 1), Gabathuler et al has not been made of record, therefore, any assertions about what Gabathuler et al might teach are unconvincing. Furthermore, the claims are not directed to an intact E3/19K protein. Therefore, the function of such a protein in nature to sequester MHC molecules in the secretory pathway (emphasis added) does not mitigate against the rejection in light of the prior art teachings made of record and discussed extensively in previous Office Actions.

Regarding 2), peptides associated with MHC molecules are broadly considered "secreted", despite applicants assertions and protests to the contrary. This is because they are processed through the same general secretory pathway (i.e. ER, Golgi, etc. See Alberts et al, pages 599-601) as all molecules ultimately bound for what is considered "outside" the cell. The only reason MHC molecules remain bound to the cell are their transmembrane domains, which serve as an anchor (see Fig. 4.11 from Janeway et al for an illustration). Molecules without such a transmembrane domain are released from the cell into the surrounding milieu.

Regarding 3), this statement is false on its face. As detailed by the prior art made of record, the very purpose of signal sequences are to direct proteins to the secretory pathway. Applicants offer no alternative explanation as to why a signal sequence would exist other than to direct a protein to some component of the secretory pathway. Applicants are not the first to measure secretion mediated by the E19 signal sequence for reason of record, i.e. the teachings of Restifo et al. Because the peptide:MHC complexes of Restifo et al remain attached to the cell surface does not mean they are not secreted, as applicants mistakenly assert, see the explanation above. Applicants further ignore the evidence that antiangiogenic proteins can be expressed and secreted using signal sequences other than those "naturally" associated with the antiangiogenic protein, and that such relatively large proteins are not bound by MHC molecules (which bind small peptides, not proteins).

Regarding 4), a review of Li et al reveals no such statement.

Regarding 5), a review of the prosecution of this application reveals no such statement by the Examiner. Certain art which applicant relies upon (e.g. Hegde et al) has not been made of record and thus any teachings within not considered. Regarding Martoglio et al, it is not clear, and applicants do not explain, why the discussion of signal sequences and their efficiency mitigates against the instant rejection, which involves an adenoviral ss which has evolved to be functional in human cells, and is evidenced by the art of record to secrete heterologous proteins.

Regarding 6), this is, again, a statement of opinion that is false on its face and completely ignores the facts and evidence found in the teachings of Restifo and Li et al. The E19 signal sequence, again, was used to direct expression and secretion of given peptides, even if said peptides were in a complex with MHC molecules that remain bound to the cell surface. See the explanation above.

Regarding 7), again, this is an intended use limitation and has been addressed previously. Applicants present a paragraph of arguments regarding this issue, but nothing in these arguments details what exactly the structural limitation imposed by this intended use might be. These arguments are also silent regarding how the asserted "functional" limitation is to be interpreted into a structural limitation other than those limitations already addressed by the Examiner. The composition taught by the prior art meets all the structural limitations of the claims, and thus meets the intended use limitation. A "reasonable expectation of success" is not a structural limitation, but rather is a policy consideration in 35 USC 103 rejections. Given the highly advanced state of the art, and the lack of a basis of comparison (see below), it has been considered throughout prosecution that a reasonable expectation of success is present. Applicants have confused this standard with an absolute certainty of success, which does not appear to be a possibility in 35 USC 103 rejections. Absent evidence to the contrary, the use of the adenoviral E19 ss sequence to express an antiangiogenic protein in the context of an adenoviral vector would result in increased levels of circulating antiangiogenic protein relative to organisms/animals that did not receive the adenoviral vector, or received a control vector not expressing the antiangiogenic protein. The results of Griscelli et al, and applicants Exhibit C (submitted with the Pasqualini declaration, 12/14/2007), page 1018, third column, first full , teach the general reduction in tumor size upon administration of viral vectors expressing antiangiogenic proteins.